REMARKS

As a preliminary matter, the Applicant wishes to thank Examiners Lucas and Housel for the courtesy of an interview, which was granted to the undersigned and inventor Derek O'Hagan on April 24, 2003. Receipt of the Interview Summary setting forth the substance of the interview is acknowledged.

A. Status of the Claims

Claims 1-7, 9-16, 43-47, 52-54, 56-59 and 69-103 are pending herein.

Claims 9, 52, 53 and 81-84 are directed to non-elected species. These claims have not been deleted at this time, however, because they are to be entitled to consideration in the event of allowance of the generic independent claims from which they depend, as provided by MPEP 809.02(a).

Support for forming a microparticle and exposing the same to an antigen can be found throughout the specification. See, e.g., page 19, lines 22-25 of the present specification, the Examples, and originally filed claims 27 and 36.

Support for forming a microparticle in the presence of detergent can be found throughout the specification. See, e.g., the first paragraph of page 17.

Support for raising an immune response in a vertebrate animal using the claimed compositions can be found, for example, at page 13, lines 22 *et seq.* of the specification.

Support for tumor antigens can be found, for example, on page 10, lines 7-8.

B. Response to Office Action

1. Rejection of claim 73--35 U.S.C. 112, second paragraph

Claim 73 is rejected under 35 U.S.C. 112, second paragraph, as indefinite based on the recitation of the phrase "pathogenic antigen." This phrase has been replaced with the phrase --pathogenic organism-- to provide appropriate antecedent basis.

Reconsideration and withdrawal of the rejection of claim 73 under 35 U.S.C. 112, second paragraph are respectfully requested.

2. Rejection of claims 1, 4, 5, 7, 43, 46 and 78, 35 U.S.C. 102(a)

Claims 1, 4, 5, 7, 43, 46 and 78 are rejected under 35 U.S.C. 102(a) as anticipated by Levy et al. (WO 96/20698). The Applicants respectfully traverse this rejection and its supporting remarks.

Independent claim 43 is presently directed to a microparticle comprising (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle. The microparticle is formed by a process that comprises: (1) forming a microparticle comprising the polymer and the detergent, the microparticle being formed in the presence of the detergent; and (2) exposing the microparticle to the antigen.

Independent claim 1 is similar to claim 43, except that the polymer is specified to be selected from a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate.

The Applicants have found that providing a microparticle that comprises a cationic and/or anionic detergent in addition to a biodegradable polymer results in improved adsorption of the antigen to the biodegradable polymer. See, e.g., the present specification at page 3, line 19 to page 4, line 2.

Levy et al., on the other hand, does not describe a microparticle comprising the combination of (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle by exposing a microparticle to an antigen as claimed.

Instead, Levy et al. teaches surface-modified biodegradable controlled release nanoparticles as sustained release bioactive agent delivery vehicles. *See* Levy et al. Abstract. The nanoparticles are a core of biodegradable, biocompatible polymer. *See Id.* at page 6, lines 13 *et seq*. The polymeric core may have a bioactive agent or combination of agents incorporated, embedded, entrained or otherwise made part of the polymeric matrix comprising the nanoparticle core. *See Id.* at page 7, lines 1-3. The incorporated bioactive agent is released as the polymer hydrolyzes and dissolves, thereby biodegrading. *See Id.* at page 7, lines 3-4. Hence, Levy et al., taken as a whole, is

directed to particles having entrapped bioactive agents, which are made part of a polymer core and are released upon biodegradation of the polymer core.

Consistent with the above, the disclosure at pages 34-35 of Levy et al. (Example 4) referred to in the Office Action is directed to a method for incorporating a hydrophilic bioactive agent, ibutilide, into PLGA nanoparticles. Thus, in contrast to the antigens presently claimed in claims 1 and 43, the bioactive agent, ibutilide, in Example 4 at pp. 34-35 of Levy et al. is not *adsorbed* to the surface of the nanoparticles, but rather is *incorporated into* the nanoparticles. See, e.g., page 34, lines 16-17. See also page 35, lines 13-15: "Since the complex [of palmitic acid and ibutilide] is also ionic, it will separate again, *during bioerosion*, into drug and fatty acid to release drug from the nanoparticles." (Emphasis added.)

Moreover, this Example fails to disclose the use of an antigen as claimed, but rather is directed to ibutilide, which is an *anti-arrhythmic compound*.

"To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001). The disclosure in Levy et al. pointed to in the Office Action (i.e., Example 4, pp. 34-35) clearly fails to meet these criteria. Accordingly, it is respectfully submitted that Levy et al do not anticipate claims 1 and 43.

Applicants further maintain their prior contention that Levy et al. is not enabling as a reference, because Levy et al. does not teach or suggest how to make the presently claimed invention. For example, as noted above, the teachings of Levy et al. are generally directed to particles having entrapped bioactive agents, which are made part of a polymer core and are released upon biodegradation of the polymer core, as opposed to microparticles with adsorbed bioactive agent as claimed.

For at least the above reasons, it is respectfully submitted that Levy et al do not anticipate independent claims 1 and 43. Moreover, claims 4, 5, 7, 46 and 78, which are dependent upon these independent claims, are also not anticipated by Levy et al. for at least the above reasons as well.

Therefore, reconsideration and withdrawal of the rejection of claims 1, 4, 5, 7, 43, 46 and 78 under 35 U.S.C. 102(a) as being anticipated by Levy et al. are respectfully requested.

3. Claims 1-7, 11, 13, 14, 43-47, 54, 56, 57, 75, 76 and 78--35 U.S.C. 103(a)

Claims 1-7, 11, 13, 14, 43-47, 54, 56, 57, 75, 76 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Unger et al., U.S. Patent No. 5,830,430, or alternatively in view of Bertling et al., *Biotech and App. Biochem.*, 13: 390-405. The Applicants respectfully traverse this rejection and its supporting remarks.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. 103, (a) there must be some suggestion or motivation to modify/combine the references of record, and (b) there must be a reasonable expectation of success. See MPEP §2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.* The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination or modification. MPEP 2143.01 (emphasis added) (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

As noted above, independent claim 43 is presently directed to a microparticle comprising (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle. The microparticle is formed by a process that comprises: (1) forming a microparticle comprising the polymer and the detergent, the microparticle being formed in the presence of the detergent; and (2) exposing the microparticle to the antigen. Independent claim 1 is similar to claim 43, except that the polymer is specified to be selected from a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate.

Claims 1 and 43 are neither taught nor suggested by Levy et al. In this regard, the Applicants wish to reiterate that a remarkably wide range of surface modifying agents are listed in the paragraphs spanning page 13, line 8 to page 15, line 15 of Levy et al. in addition to cationic and anionic surfactants, including synthetic polymers, biopolymers, low molecular weight oligomers, natural products and nonionic surfactants. Due to the immense number of these agents that are set forth in Levy et al., it is respectfully submitted that, without the benefit of hindsight, the chances of one or ordinary skill in the

art arriving at the combination of elements as presently clamed in claims 1 and 43 are exceedingly remote.

The Office Action recognizes that the presently pending claims are not obvious in view of the Levy et. al., but contends that one of ordinary skill in the art, upon reading Levy et al. in combination with either Unger et al. or Bertling et al., would have found it obvious to use cationic detergents to bind negatively charged bioactive agents and vice versa, and would have had a reasonable expectation of success.

Applicants respectfully disagree.

Turning first to Unger et al., this reference is directed to cationic lipid compounds that are suitable for use as carriers for the intracellular delivery of bioactive agents, for example, in connection with *liposomes* (see Unger et al. Abstract and col. 2, lines 30-63). This is in contrast to *microparticles* as claimed.

Moreover, rather forming a carrier from a *combination* of a cationic/anionic species (i.e., a detergent) with another species (i.e., a biodegradable polymer) as claimed, the carrier is Unger et al. is said to be a single species (i.e., a lipid compound) having one or more cationic *groups*. See Unger et al. Abstract, col. 5, lines 13 *et seq.*, and col. 16, lines 54 *et seq.*

As a result, it is not seen what, if anything, a person of ordinary skill in the art would be motivated to do upon reading Unger et al. and Levy et al. However, it is clear that such a person would not find motivation to create a microparticle comprising a biodegradable polymer and a cationic and/or anionic detergent as claimed.

The combination of Levy et al. in view of Bertling et al. is also deficient. Bertling et al. teaches nanoparticles prepared from butyl 2-cyanoacrylate and DEAE-dextran (i.e., diethylaminoethyl-dextran) to which DNA is bound.

However, DEAE-dextran is not a cationic detergent for purposes of the present rejection. In this regard, note that DEAE-dextran is not categorized as a cationic detergent in Levy et al. (see page 15, lines 1-15), but rather is listed two pages prior (i.e., at page 13, lines 10-17) as a synthetic polymer surface modifying agent.

Moreover, Bertling et al. reports that DNA transferred by nanoparticles *is not transcriptionally active* (see p. 399 and p. 403). Therefore, upon reading Bertling et al.,

one of ordinary skill in the art would actually have been *dissuaded* from adsorbing DNA as an antigen on the surface of a microparticle as claimed in claims 1 and 43.

For at least the above reasons, the combination of Levy et al. with either Unger et al. or Bertling et al. would not have motivated one of ordinary skill in the art to provide microparticles comprising a combination of biodegradable polymer, a cationic/anionic detergent, and an adsorbed antigen as claimed in independent claims 1 and 43.

Furthermore, Applicants also maintain that one of ordinary skill in the art would not have reasonably expected success with regard to the combination of Levy et al. in view of Unger et al. or Bertling et al. Nonetheless, and as discussed in more detail in the previous Amendment and Response of 30 September 2002, Applicants' efforts have certainly been successful and surprisingly so, even relative to the use of microparticles containing emulsion stabilizers and nonionic surfactants.

For at least the above reasons, it is respectfully submitted that claims 1 and 43 are patentable over Levy et al. in view of Unger et al. or Bertling et al. under 35 U.S.C. 103(a).

At least because they are dependent upon claim 1 or claim 43, claims 2-7, 11, 13, 14, 44-47, 54, 56, 57, 75, 76 and 78 are likewise patentable over Levy et al. in view of Unger et al. or Bertling et al.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-7, 11, 13, 14, 43-47, 54, 56, 57, 75, 76 and 78 under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of either Unger et al. or Bertling et al. are respectfully requested.

4. Claims 58 and 59--35 U.S.C. 103(a)

Claims 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of either Unger et al. or Bertling et al. and further in view of U.S. Patent No. 5,630,922 to Eswarakkrishnan et al. and U.S. Patent No. 4,534,996 to Rembaum. The Applicants respectfully traverse this rejection and its supporting remarks.

As noted above, in order to establish a *prima facie* case of obviousness under 35 U.S.C. 103, (a) there must be some suggestion or motivation to modify/combine the references of record, and (b) there must be a reasonable expectation of success. See

MPEP §2143. As also noted above, independent claims 1 and 43 are presently patentable over Levy et al. in view of either Unger et al. or Bertling et al. under this standard.

Eswarakkrishnan (which is directed to electrodepositable compositions and is cited to demonstrate that hexadecyltrimethyl-amonium bromide was a known cationic detergent) and Rembaum (which is directed to hybrid microspheres and is cited to demonstrate that sodium dodecyl sulfate was a known anionic detergent) do not make up for the above-noted deficiencies in Levy et al., Unger et al. and Bertling et al. Hence, it is respectfully submitted that claims 1 and 43 are patentable over Levy et al. in view of either Unger et al. or Bertling et al. and further in view of Eswarakkrishnan et al. and Rembaum.

At least because they are dependent upon claim 1, claims 58 and 59 are likewise patentable over Levy et al. in view of either Unger et al. or Bertling et al. and further in view of Eswarakkrishnan et al. and Rembaum.

Reconsideration and withdrawal of the rejection of claims 58 and 59 under 35 U.S.C. 103(a) are therefore requested. In this regard, it is noted that although a number of references have been applied against these claims, they continue to be unobvious.

5. Claims 69-74, 79, 80 and 85-90—35 U.S.C. 103(a)

Claims 69-74, 79, 80 and 85-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of either Unger et al. or Bertling et al. The Applicants respectfully traverse this rejection and its supporting remarks.

As noted above, independent claims 1 and 43 are presently patentable over Levy et al. in view of either Unger et al. or Bertling et al. Claims 69-74, 79, 80 and 85-90 contain all the limitations of claim 1 or claim 43. Therefore, claims 69-74, 79, 80 and 85-90 are also patentable over Levy et al. in view of either Unger et al. or Bertling et al. for at least the same reasons.

Reconsideration and withdrawal of the rejection of claims 69-74, 79, 80 and 85-90 under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of either Unger et al. or Bertling et al. are thus respectfully requested.

6. Rejection of claim 10--35 U.S.C. 103(a)

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Moore et al. (Vaccine, 13/18: 1741-1749, 1995) and Haynes et al. (AIDS Research and Retroviruses, 10, Suppl. 2:S42-S45, 1994).

As noted above, independent claim 1 is presently patentable over Levy et al. Claim 10 depends from claim 1 and is therefore patentable over Levy et al. for at least the same reasons as is claim 1. In this connection, it is noted that Moore et al. teaches the use of entrapped antigen and the use of PVA, while Haynes et al. concerns gold microparticles to which DNA is bound by polymer. Neither Moore et al. nor Haynes et al. makes up for the above-noted deficiencies in Levy et al. As a result, it is respectfully submitted that claim 10 is patentable over Levy et al. in view of Moore et al. and Haynes et al.

For at least this reason, reconsideration and withdrawal of the rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Moore et al. and Haynes et al. are requested.

7. Rejection of claims 10, 12 and 15--35 U.S.C. 103(a)

Claims 10, 12 and 15, are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Cleland et al. (U.S. Patent No. 5,643,605).

As noted above, independent claim 1 is presently patentable over Levy et al. Claims 10, 12 and 15 depend from claim 1 and are therefore patentable over Levy et al. for at least the same reasons as is claim 1. Cleland et al., which teaches microspheres having encapsulated antigen, does not make up for the above-noted deficiencies in Levy et al. Hence, it is respectfully submitted that claim 10, 12 and 15 are patentable over Levy et al. in view of Cleland et al.

Reconsideration and withdrawal of the rejection of claims 10, 12, and 15 under 35 U.S.C. 103(a) are therefore requested.

8. Rejection of claim 16 under 35 U.S.C. 103(a)

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Cox et al.

(U.S. Patent No. 5,902,565) or (b) Levy et al. in view of Cleland et al. and further in view of Cox et al.

As noted above, independent claim 1 is presently patentable over Levy et al. Claim 16 depends from claim 1 and is therefore patentable over Levy et al. for at least the same reasons as is claim 1. Moreover, as also noted above, Moore et al., Haynes et al. and Cleland et al. do not make up for the above-noted deficiencies in Levy et al. The same is true of Cox et al., which is cited for its teaching of aluminum phosphate as an adjuvant. Hence, it is respectfully submitted that claim 16 is patentable over these references.

Reconsideration and withdrawal of the rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Cox et al. or (b) Levy et al. in view of Cleland et al. and further in view of Cox et al. are thus requested.

9. Rejection of claim 58 under 35 U.S.C. 103(a)

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Carlo et al. (U.S. Patent No. 4,413,057) or (b) Levy et al. in view of Cleland et al. and further in view of Carlo et al.

As noted above, independent claim 1 is presently patentable over Levy et al. Claim 58 depends from claim 1 and is therefore patentable over Levy et al. for at least the same reasons as is claim 1. Moreover, as also noted above, Moore et al., Haynes et al. and Cleland et al. do not make up for the above-noted deficiencies in Levy et al. The same is true of Carlo et al., which teaches extraction of polysaccharides from bacteria using hexadecyltrimethylammonium hydroxide as a cationic detergent. Hence, it is respectfully submitted that claim 58 is patentable over these references.

Reconsideration and withdrawal of the rejection of claim 58 under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Carlo et al. or (b) Levy et al. in view of Cleland et al. and further in view of Carlo et al. are thus requested.

10. Rejection of claim 59 under 35 U.S.C. 103(a)

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Macfarlane (U.S. Patent No. 5,010,1834,413,057) or (b) Levy et al. in view of Cleland et al. and further in view of Macfarlane.

As noted above, independent claim 1 is presently patentable over Levy et al. Claim 59 depends from claim 1 and is therefore patentable over Levy et al. for at least the same reasons as is claim 1. Moreover, as also noted above, Moore et al., Haynes et al. and Cleland et al. do not make up for the above-noted deficiencies in Levy et al. The same is true of Macfarlane, which teaches the use of sodium dodecyl sulfate as an anionic detergent for purifying DNA. Hence, it is respectfully submitted that claim 59 is patentable over these references.

Reconsideration and withdrawal of the rejection of claim 59 under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Macfarlane or (b) Levy et al. in view of Cleland et al. and further in view of Macfarlane are thus requested.

11. Rejection of claim 77 under 35 U.S.C. 103(a)

Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of either Unger et al. or Bertling et al. and further in view of U.S. Patent No. 5,783,567 to Hedley et al. The Applicants respectfully traverse this rejection and its supporting remarks.

As noted above, independent claim 1 is presently patentable over Levy et al. in view of either Unger et al. or Bertling et al. Claim 77 depends from claim 1 and is therefore patentable over Levy et al. in view of either Unger et al. or Bertling et al. for at least the same reasons as is claim 1. Hedley et al., which is cited for its disclosure of a particle between 1.1 and 10 microns, does not make up for the above-noted deficiencies in Levy et al., Unger et al. and Bertling et al. Hence, it is respectfully submitted that claim 77 is patentable over Levy et al. in view of either Unger et al. or Bertling et al. and further in view of Hedley et al.

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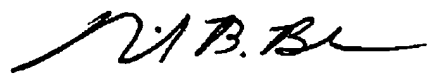
Reconsideration and withdrawal of the rejection of claim 77 under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of either Unger et al. or Bertling et al. and further in view of Hedley et al. are thus requested.

CONCLUSION

Applicants submit that claims 1-7, 9-16, 43-47, 52-54, 56-59 and 69-103 are in a condition for allowance, early notification of which is earnestly solicited. The Examiner is encouraged to telephone the Applicant's attorney at (703) 433-0510 in order that any outstanding issues be resolved.

Please continue to send all correspondence to Chiron Corporation.

Respectfully submitted,



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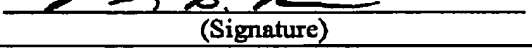

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